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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/816,790	03/22/2001	Keith D. Allen	R-855	5557

26619 7590 11/15/2004

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EXAMINER	
QIAN, CELINE X	
ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 11/15/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/816,790	ALLEN ET AL.	
	Examiner	Art Unit	
	Celine X Qian	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 September 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *40-44 and 46-50* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *40-44 and 46-50* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *22 March 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 40-44, 46-50 are pending in the application.

This Office Action is in response to the Amendment filed on 9/26/03.

Response to Amendment

The rejection of claims under 35 U.S.C.112 1st paragraph has been withdrawn in light of Applicant's amendment of the claims.

Claims 40-44, 46-50 are rejected under 35 U.S.C.101/112 for reasons discussed below.

New Grounds of Rejection

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 40-44, 46-50 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a substantial, specific and credible asserted utility or a well-established utility.

The claims are drawn to a transgenic mouse whose genome comprises a disruption in an endogenous sulfotransferase gene, wherein the disruption is homozygous, the transgenic mouse lacks production of functional sulfotransferase protein and exhibits, relative to a wild type mouse, behavioral abnormality such as aggressive behavior, hyperactivity and decreased anxiety. The claims are further drawn to a cell or tissue isolated from said mouse, a targeting construct for generating disruption of the sulfotransferase gene, a murine embryonic stem cell comprising a disruption of the sulfotransferase gene, and a method for producing said mouse.

No well-established utility exists for the claimed transgenic mouse. However, the specification asserts or implies the following as credible, specific and substantial patentable utilities for the claimed transgenic knockout mouse and cells or tissues isolated from said mouse:

1) To be used in methods of identifying agents capable of affecting a phenotype of said mouse.

2) To identify agents useful as therapeutic agents for treating conditions associated with a disruption or other mutation of the sulfotransferase gene.

3) To identify agents having an effect on sulfotransferase expression or function.

4) To serve as models for diseases.

5) To test and develop new treatments relating to the behavioral phenotypes.

Each of the following shall be addressed in turn:

1) *To be used in methods of identifying agents capable of affecting a phenotype of said mouse.* This utility is credible, specific but not substantial because the specification does not disclose a utility for such agents. The phenotype of behavioral abnormality is resulted from the disruption of a single gene sulfotransferase, however, such genotypic-phenotypic association is not known in the art for relating to a specific disease. Although the agents can affect a phenotype in said transgenic mouse or a cell/tissue isolated from said mouse, the utility is not substantial because there is no other use of said agents except affecting a phenotype only exists in a mouse model. Since this asserted utility is not presented in mature form so it could be readily used in a real world sense, the asserted utility is not substantial.

2) *To identify agents useful as therapeutic agents for treating conditions associated with a disruption or other mutation of the sulfotransferase gene.* This utility is not credible, specific

or substantial because the specification does not disclose what kind of conditions is associated with a disruption or other mutations of the sulfotransferase gene. In addition, the specification fails to disclose what specific condition(s) the identified agents can treat. Since this asserted utility is not presented in mature form so it could be readily used in a real world sense, the asserted utility is not credible, specific and substantial.

3) *To identify agents having an effect on sulfotransferase expression or function.* This asserted utility is specific but not credible and substantial because the specification does not disclose 1) how to use a mouse or cell that does not express sulfotransferase to identify agents which affect the gene expression or function; 2) how to use such identified agents that affect sulfotransferase expression or function. Since the identified agents does not have a substantial utility, the claimed mouse or mouse cells used in a method for identifying such agents does not have substantial utility as well. This asserted utility is not credible since there is no expression or function can be monitored in the knockout mouse or cells/tissues isolated from said mouse, it is unclear how these agents that affect sulfotransferase expression/function can be identified.

4*) To serve as models for diseases.* The asserted utility is substantial but not credible and specific because the specification does not disclose what types of disease the transgenic mouse or cells/tissues isolated from said mouse represents.

5) *To test and develop new treatments relating to the behavioral phenotypes.* This utility is not credible, substantial and specific (see reasons discussed in the 112 1st paragraph rejection). Since this asserted utility is not presented in mature form so it could be readily used in a real world sense, the asserted utility is not credible, specific or substantial.

Since the claimed transgenic mouse and cells/tissues isolated from said mouse does not have utility, a method of producing said transgenic mouse does not have utility either. Therefore, the claimed invention lacks patentable utility for reasons given above.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 40-44, 46-50 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific, substantial and credible asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to: (a) the nature of the invention; (b) the breadth of the claims; (c) the state of the prior art; (d) the amount of direction provided by the inventor; (e) the existence of working examples; (f) the relative skill of those in the art; (g) whether the quantity of experimentation needed to make or use the invention based on the content of the disclosure is "undue"; and (h) the level of predictability in the art (MPEP 2164.01 (a)).

Nature of the Invention:

Claims 40-44, 46-50 are drawn a transgenic mouse comprising a disruption in the sulfotransferase gene, wherein the disruption is homozygous, the mouse does not produce

functional sulfotransferase protein, and exhibits an abnormal behavior such as aggressive behavior, hyperactivity and decreased anxiety, relative to a wild type mouse. The claims are further drawn to a cell or a tissue isolated from said transgenic mouse, and a method of producing said transgenic mouse.

Breadth of claims and amount of guidance in the specification and working Examples:

In the instant case, the claims encompass both heterozygous and homozygous sulfotransferase transgenic knockout mouse, wherein when the disruption is homozygous, it exhibits abnormal behavior. The specification does not provide an enabling disclosure for how to use the transgenic mouse as claimed. The specification does not provide specific teaching on how to use the transgenic knockout mouse without a phenotype or with a transgene independent phenotype. Further, the specification fails to teach how to use the transgenic mouse with the disclosed phenotype of abnormal behavior. The specification only prophetically teaches that the transgenic mouse can serve as models for diseases, screening drugs for treating the disease, screening agents that modulates a phenotype of said mouse, or screening agents that modulate the function or expression of the sulfotransferase. However, the specification fails to teach what type of diseases are associated with the disclosed genotypic vs. phenotypic correlation, or the phenotype exhibited by the transgenic knockout mouse. As such, whether the sulfotransferase transgenic knockout mouse can serve as any disease model or screening drugs to treat disease is unpredictable. Likewise, whether cells or tissues isolated from said mouse can be used for this purpose is unpredictable. The specification also fails to teach how to use an agent that modulates the phenotype associated with sulfotransferase gene disruption. In addition, the specification fails to teach how to screen agents that affect the expression or function of the sulfotransferase

the in a mouse (or cells or tissues isolated from said mouse) does not express said gene. As such, one skilled in the art would not know how to use the transgenic mouse without any phenotype (i.e. heterozygotes) or with the phenotype of abnormal behavior for the above embodiments. Similarly, one skilled in the art would not know how to use the cells or tissues isolated from said mouse. As such, the specification does not provide sufficient guidance for the enablement of the claimed mouse.

The state of art and the level of predictability in the art:

The prior art teaches that the phenotype of a transgenic or knockout animal is highly unpredictable. When considering the predictability of the phenotype of a transgenic mouse, one has to remember that the phenotypes examined in transgenic and knockout models are influenced by the genetic background in which they are studied and the effect of allelic variation and the interaction between the allelic variants (pg.1425, paragraph 1 in Sigmund, C.D. 2000. Arterioscler Thromb Vasc Biol.20:1425-1429). Sigmund indicate that the genetic background is the collection of all genes present in an organism that influences a trait or traits. These genes may be part of the same biochemical or signaling pathway or of an opposing pathway or may appear unrelated to the gene being studied. Such genetic background and "epigenetic" effects, such as allelic variants between different strains of mouse, can dramatically alter the observed phenotype. Moreover, the particular genetic elements required for expression varies from species to species. For example, Jacks et al. (1992) describe Rb KO mice that do not display retinoblastoma; rather they exhibit the unexpected phenotype of pituitary tumors. The pituitary tumors arise from cells lacking a wild-type Rb allele. Thus, tumors were found to arise not in retinas, as in humans, but in the pituitary gland (page 299, Discussion, paragraphs 1 and 3). The

specification does not teach any function of the sulfotransferase gene. The phenotype exhibited by the homozygous sulfotransferase gene knockout mouse is behavioral abnormality. The disclosed phenotype of said knockout mouse is cannot predict sulfotransferase gene function in human for reasons given above. As such, without teaching from the specification, one skilled in the art would not know how to use the claimed mouse with aggressive behavior, hyperactivity and decreased anxiety since this phenotype only existed in mouse. Whether human with abnormal behavior such as aggressive, hyperactivity and decreased anxiety is result from the disruption of the sulfotransferase gene is unpredictable. Therefore, whether the claimed mouse can be served as a disease model or screening drugs or treatments is unpredictable. Similarly, whether cells or tissues isolated from said mouse can be used for this purpose is also unpredictable.

Moreover, the claims encompass both heterozygotes and homozygotes. Claims 40-44 and 46-59 encompass heterozygotes. However, since heterozygotes have one functional allele, the heterozygotes would not be expected to have the same phenotype as the homozygotes. The specification does not teach whether the heterozygotes have the same phenotype as the homozygotes. As such, the phenotype of a heterozygotes is unpredictable, and the specification, in the instant case, is not enabling for a transgenic knockout mouse that exhibits no phenotype or that exhibits transgene-independent phenotypes.

The state of art at the time of filing considers generating null mutation of a specific gene in mice and phenotypic behavior resulted from the mutation as unpredictable. Crawley et al. (1997, Psychopharmacology, Vol 132, pages 107-124) teaches that the phenotype of a mutant mouse is not only the result of the targeted gene, but it also reflects interactions with background

gene, and other unknown mutations in the genetic background (see pages 107 last paragraph through page 108 1st paragraph). The article further teaches that not all isogenic backgrounds are appropriate for a given study, since the behavioral characteristics of certain isogenic strains could overshadow the effects of the targeted mutations (see page 108, 1st col., lines 10-14). Moreover, two strains commonly used in ES cell and knockout generation C57BL/6 and various substrains of 129 are unusual on many standard behavioral paradigms. The unique traits of 129 and C57BL/6 mice are examples of a widespread problem for interpretation of behavioral phenotypes of null mutations, given the genetic diversity that exists amongst the dozens of other commonly available inbred mouse strains (see page 108, 2nd paragraph). Therefore, whether the behavioral phenotype is result from null mutation alone is unpredictable. As such, whether the claimed mouse can be used to develop new treatments for behavioral phenotype is unpredictable.

The state of art at the time of the filing is silent on a transgenic mouse whose genome comprises a disruption in an endogenous sulfotransferase gene, wherein the disruption is homozygous, said mouse lacks production of the sulfotransferase protein, and said mouse exhibits phenotypic feature of behavioral abnormality, as compared to a wild type mouse. The art is also silent on what type of disease is related to sulfotransferase dysfunction that would result in the disclosed phenotype. As such, whether transgenic mouse exhibits phenotype of abnormal behavior can be used for a disease model or screening for drugs is unpredictable. Since the mouse is not enabled, the cell or tissue isolated from the mouse and method for producing said mouse are not enabled either. Without teaching from the art and lack of sufficient guidance from the specification, one skilled in the art would have to engage in undue

experimentation to use the inventions as claimed. Therefore, the claimed inventions are not enabled by the instant specification.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Celine X Qian whose telephone number is 571-272-0777. The examiner can normally be reached on 9:30-6:00 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel Ph.D. can be reached on 571-272-0781. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Celine Qian, Ph.D.